COMPARISON OF RACEMIC ALBUTEROL AND LEVALBUTEROL FOR TREATMENT OF ACUTE ASTHMA

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Objective To determine whether levalbuterol resulted in fewer hospital admissions than racemic albuterol when used for treatment of acute asthma.

Study design A randomized, double-blind, controlled trial was conducted in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital. Children age 1 to 18 years (n = 482) provided a total of 547 enrollments. Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum six doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome.

Results Hospitalization rate was significantly lower in the levalbuterol group (36%) than in the racemic albuterol group (45 %, $P = .02$). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95% confidence interval, 1.01-1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; $P = .63$). No significant adverse events occurred in either group.

Conclusions Substituting levalbuterol for racemic albuterol in the ED management of acute asthma significantly reduced the number of hospitalizations. *(J Pediatr 2003;143:731-6)*

See editorial, p 702.

Inhaled β_2-agonist agents are widely used to treat bronchospasm in acute asthma exacerbations. In combination with systemic corticosteroids, repeated administration of inhaled β_2-agonists is a primary treatment in most status asthmaticus treatment algorithms. The predominant bronchodilator in current use is the β_2-selective agonist racemic albuterol, a 50:50 mixture of (R)-enantiomers and (S)-enantiomers.[1] Levalbuterol, (R)-albuterol, demonstrates 100-fold more potent β_2-receptor binding than (S)-albuterol and is responsible for the bronchodilator effects of the racemate. The ability to separate the isomers of β_2-agonists has challenged previous assumptions that (S)-albuterol is inert. In vitro, (S)-albuterol has been demonstrated to increase intracellular Ca^{2+} [2,3] and stimulate eosinophil recruitment and degranulation.[4,5] (S)-albuterol has essentially no bronchodilator activity but different pharmacokinetics that result in a prolonged plasma half-life.[6] The in vivo effects of (S)-albuterol are more controversial, with some data suggesting enhancement of bronchoconstriction by as yet poorly understood mechanisms, and data from other studies failing to support an antitherapeutic effect.[7-12] Pediatric levalbuterol studies have demonstrated improvement in forced expiratory flow in 1 second at less than half the dose of racemic albuterol and have suggested a lower adverse effect profile.[13,14] However, these data were obtained from stable pediatric patients, and clinical relevance to the acute setting has not been supported by large-scale trials. Potential adverse effects caused by (S)-albuterol or positive effects of levalbuterol would be most apparent in

ACA	Asthma care algorithm	GEE	Generalized estimating equation
ACU	Asthma care unit	LOS	Length of stay
CI	Confidence interval	PICU	Pediatric intensive care unit
ED	Emergency department		

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a setting of repeated drug administration. It was our hypothesis that levalbuterol, when administered frequently for the treatment of status asthmaticus, would result in fewer hospitalizations and more rapid improvement than treatment with racemic albuterol.

METHODS

Study Population

All children between 1 and 18 years of age with physician-diagnosed asthma presenting to the Pediatric Emergency Department (ED) of Rainbow Babies and Children's Hospital, a university-affiliated tertiary care children's hospital in Cleveland, Ohio, between April 2000 and December 2000 for treatment of acute asthma were eligible for study enrollment. Patients were not eligible if they were experiencing a first episode of wheezing, were not currently being treated for asthma, were pregnant, had known hypersensitivity to albuterol, or had cystic fibrosis, cyanotic or uncorrected congenital heart disease, chronic neonatal lung disease, or other chronic obstructive pulmonary diseases. Patients treated at other institutions before ED presentation were not included. Admission to the pediatric intensive care unit (PICU) ended treatment with the study medications. The Institutional Review Board of University Hospitals of Cleveland approved this study, and written informed consent was obtained from a parent or guardian or patient (one patient age 18 years signed his own consent).

Recruitment and Randomization

On ED triage and study enrollment, patients were assigned by computer-generated block randomization, stratified by age (<6 years or ≥6 years), to receive, in double-blinded fashion, aerosol therapy consisting of preservative-free, unlabeled, identical-appearing unit dose vials of 1.25 mg levalbuterol ([R]-albuterol) or 2.5 mg racemic albuterol (1.25 mg [R]-albuterol and 1.25 mg [S]-albuterol). Identical-appearing numbered packets (sequence provided by a statistician) containing all study medications and data collection forms were provided to the ED physicians, who enrolled the patients. Sepracor provided both products from lots manufactured for commercial use in compliance with all Food and Drug Administration regulations and independently tested for purity and concentration.

Emergency Department Asthma Care Algorithm

At Rainbow Babies and Children's Hospital, acute asthma exacerbations are treated according to a standardized, assessment-driven ED-asthma care algorithm (ACA). Study drugs were administered by using small-volume nebulizer devices (Nebutech, Salter Labs, Irvine, Calif). Patients <6 years old received nebulized treatments via face mask, whereas those ≥6 years old received them via mouthpiece. Patients received nebulized treatments at 20-minute intervals until they either met discharge criteria or reached a maximum of six treatments within 2 hours, at which time they were admitted.[15] Oral prednisone (2 mg/kg/d, 60 mg maximum) was administered to patients failing to meet discharge criteria after the first ED-administered aerosol treatment. Supplemental oxygen was provided to patients to maintain oxyhemoglobin saturation ≥94%. Patients who presented with or developed severe respiratory distress defined by previously described chest assessment score[16] (poor air exchange, severe or absent wheeze, accessory muscle use, oxygen saturation <93%) during ED-ACA treatment received a standardized intensification regimen consisting of aerosolized ipratropium (500 μg) plus study drug and subcutaneous epinephrine (0.01 mg/kg, maximum 0.3 mg). Patients making insufficient clinical improvement on the ED-ACA to allow entry to phase I of the inpatient ACA (assessment and treatment every 2 hours) were admitted to the PICU. Patients admitted to the inpatient ACA continued treatment with the same nebulized β_2-agonist study drug and nebulizer to which they were randomized during the ED-ACA study. The decision to admit a patient was made by the ED attending physician, who used the standard ED-ACA criteria for admission and was not involved in study design or data analyses.

Inpatient Asthma Care Algorithm

The inpatient ACA consists of four phases in which the interval between assessment and aerosol administration increases in a stepwise fashion: every 2 hours in phase I, every 3 hours in phase II, every 4 hours in phase III, and every 6 hours in phase IV.[16,17] Patients complete the inpatient ACA when they maintain discharge criteria for at least 6 hours while receiving nebulized β_2-agonist every 6 hours. Patients and parents were queried at the end of each ACA phase about adverse effects (tremor, nausea, vomiting, headache, any other concern) that occurred in the just-completed phase. Maximal heart rate occurring during each phase was also recorded.

The primary outcome measure was hospital admission rate. Secondary outcomes included inpatient length of stay (LOS), ED LOS, rate of intensification, number of aerosols, requirement for supplemental oxygen, and adverse effects.

Statistical Analysis

Sample size, estimated for the primary outcome, was calculated based on a historical cohort of ACA admissions and by using the Pearson χ^2 test. To detect a reduction in hospitalization rate from 42% (average admission rate, past 5 years, for asthma at our hospital) to 30%, 266 subjects were needed for randomization to each group, assuming 80% power and a significance level of .05. No interim analyses were planned.

Baseline characteristics were summarized by drug group by using means, SDs, medians, frequencies, and percentages as appropriate. Methods designed to handle the correlation in outcome in successive enrollments of the same child were used. Baseline comparisons between drug groups were performed by using generalized estimating equations (GEEs)[18,19] with an exchangeable correlation matrix and the Wilcoxon rank sum test for clustered data.[20] Hospital admission rates between

groups were tested with a GEE model assuming a binomial distribution and log link. The lengths of stay in the ED and in the hospital were compared by using GEE regression models assuming a normal distribution. Hospital LOS was log-transformed to normalize the distribution. Hospital admission rate was defined as admission to the asthma care unit (ACU) or PICU, or transfer. ED LOS was defined as the duration from ED entry to ED discharge to home, and hospital LOS was defined as the duration from hospital entry to hospital discharge for patients admitted to the hospital. GEE regression models were used to adjust for possible confounders (sex, age, race, chronic asthma severity class, oral corticosteroid use in the previous 24 hours, unscheduled ED visits or hospitalizations in the past 12 months) for admission rate and LOS, respectively. A forward stepwise approach was used to select the variables. Inpatient outcome data were not available for patients transferred to another hospital. Although children admitted to the PICU were taken off protocol, their LOS was included because all analyses followed the intent to treat principle.

RESULTS

A total of 552 enrollments from 482 children were randomized between April 2000 and December 2000; five subjects had other chronic disease and were excluded from all analyses. Another 552 children were missed by recruiters or were determined to have a questionable diagnosis of asthma. The final analyses used 547 enrollments: 278 enrollments in the levalbuterol group and 269 in the racemic albuterol group; children who were repeat enrollments were equally distributed between the treatment groups. The majority of the patients were black males with moderate to severe chronic asthma (56.5% levalbuterol; 60.8% racemic albuterol); patients in the two treatment groups had no significant differences in demographic measures (Table I). There was no significant difference between the levalbuterol and albuterol study groups in the number of patients reporting use of inhaled corticosteroids as a controller medication (P = .72) or in the use of oral corticosteroids in the 24 hours before presentation to the ED (Table I). There was no difference between study drug groups in the severity of the acute asthma episode as determined by presenting respiratory rate and arterial oxyhemoglobin saturation or number of patients requiring intensification for severe respiratory distress (Tables I and II). Two patients in each study drug group were unable to tolerate oral prednisone and received intravenous methylprednisolone. Eighteen children (20 enrollments) in the racemic albuterol group and eight children and enrollments in the levalbuterol group met criteria for hospital admission after completion of the ED-ACA but were not included in the inpatient ACA data because their insurance required that inpatient treatment be performed at other area institutions.

Significantly fewer patients in the levalbuterol group required hospital admission (Figure). The number of children with asthma presenting to the ED who would need to be treated with levalbuterol to prevent one hospitalization was 10.6 (95% CI, 5.8-71.4). The reduction in admission rate between the two study drug groups was independent of chronic inhaled corticosteroid use or acute use of oral corticosteroid.

Table I. Baseline characteristics of children who completed the study

	Racemic albuterol (n = 269)	Levalbuterol (n = 278)
Age, y (mean)	7.2 ± 4.2	7.1 ± 3.9
Range	1-17.7	1-18.4
Male	181 (67)	186 (67)
Ethnic group		
White	42 (16)	33 (12)
Black	224 (83)	244 (88)
Other	3 (1)	1 (0.4)
Initial respiratory rate	35.1 ± 12.8	35.1 ± 12.2
ED visits (past 12 months)	n = 254	n = 258
0	71 (27.9)	65 (25.2)
≥1	183 (72.1)	193 (74.8)
Hospitalizations (past 12 months)	n = 253	n = 263
0	151 (59.7)	158 (60.3)
≥1	102 (40.3)	104 (39.7)
Medication use		
Inhaled steroid	59 (21.9)	68 (24.5)
Cromolyn	42 (15.6)	68 (24.5)*
Leukotriene receptor antagonist	40 (14.9)	34 (12.2)
Long-acting β-agonist	11 (4.1)	17 (6.1)
Oral steroids in past 24 h	19/266 (7.1)	15/270 (5.6)

± Values are SDs. Numbers in parentheses are %. *P = .002.

Because recent, repeated use of β-agonists may affect the response to subsequent bronchodilators, we examined the influence of racemic albuterol use before ED presentation. (Only one patient reported using levalbuterol at home.) The use of albuterol before the ED visit was significantly associated with hospital admission rate. Controlling for study drug group, age, and oral corticosteroid use in the previous 24 hours, children who reported taking ≥2 aerosols in the past 2 hours had an approximately 40% higher hospital admission rate (relative risk [RR], 1.39; 95% CI, 1.13-1.72; P = .002). Similar results obtained for children reported to have had >3 aerosols in the past 12 hours (RR, 1.34; 95% CI, 1.09-1.65; P = .004). In a GEE regression model, after controlling for age and treatment with >3 aerosols in the past 12 hours and oral corticosteroid use in the previous 24 hours, the relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95% CI, 1.01-1.51, P = .04). Levalbuterol had a lower admission rate (43%) compared with racemic albuterol (53%). The same analysis performed for receiving ≥2 albuterol aerosols in the past 2 hours showed that the effect of study drug was similar (RR, 1.23; 95% CI, 1.00-1.52; levalbuterol admission rate, 46 %; racemic albuterol admission rate, 56%; P = .03).

Table II. Secondary outcomes in the ED and inpatient unit

Outcome	Racemic albuterol	Levalbuterol	*P*
ED			
LOS, mean h (median)	2.2 ± 0.8 (2.1)	2.3 ± 0.9 (2.2)	.25
Aerosols, mean	4.1 ± 1.9	3.7 ± 1.9	.08
Admission oxygen saturation, %	95.9 ± 2.7	95.6 ± 2.8	.36
Discharge respiratory rate	35.6 ± 12.6	37.0 ± 10.4	.26
Intensified (%)	31 (11.5)	25 (9.0)	.35
Inpatient			
LOS, mean h (median)	50.3 ± 38.8 (44.3)	44.9 ± 13.5 (44.1)	.63
Aerosols, mean	11.9 ± 4.7	11.5 ± 3.7	.61
Admission oxygen saturation, %	95.5 ± 2.5	94.2 ± 6.0	.26
Patients requiring oxygen in any phase (%)	12 (12.4)	15 (17.9)	.21
Intensified (%)	15 (16.5)	8 (10.1)	.21

± Values are SDs. ED LOS is for patients discharged to home from the ED. Inpatient LOS is the hospital LOS for patients admitted from the ED to the ACU or PICU.

The ED LOS for patients discharged from the ED to home did not differ between the two treatment groups (Table II) and was not influenced by the time from ED entry to start of ED care path, which did not differ between the groups (P = .64). Patients in the levalbuterol group required the same number of ED-administered aerosols compared with the racemic group; the number of inpatient aerosols also did not differ between the groups (Table II).

Hospital LOS for patients admitted did not differ between the groups (Table II). The number of patients admitted to the ACU who required intensified therapy was similar in the two treatment groups; there were no significant differences between groups in any other secondary outcomes (Table II). The percentage of patients admitted to the PICU was the same in both groups (levalbuterol, n = 5, 2%; racemic albuterol, n = 6, 2%).

Adverse Effects

There were no significant adverse effects seen in either the levalbuterol or racemic albuterol group in either the ED or ACU. At the end of the ED-ACA, there was no difference in the mean heart rate (130.1 ± 23.3 bpm, levalbuterol; 129.7 ± 25.5 bpm, racemic albuterol; P = .94), respiratory rate (37.0 ± 10.4 bpm, levalbuterol; 35.8 ± 12.6 bpm, racemic albuterol; P = .26), or oxyhemoglobin saturation (96.3% ± 2.5, levalbuterol; 96.3% ± 2.5, racemic albuterol; P = .81). One patient in the racemic albuterol group and one in the levalbuterol group had nausea and vomiting, and in the levalbuterol group, one patient had a rash and one had headache during the inpatient phase of treatment. Mean maximal heart rates at the end of each treatment phase of the inpatient ACA were not significantly different between the study groups (data not shown).

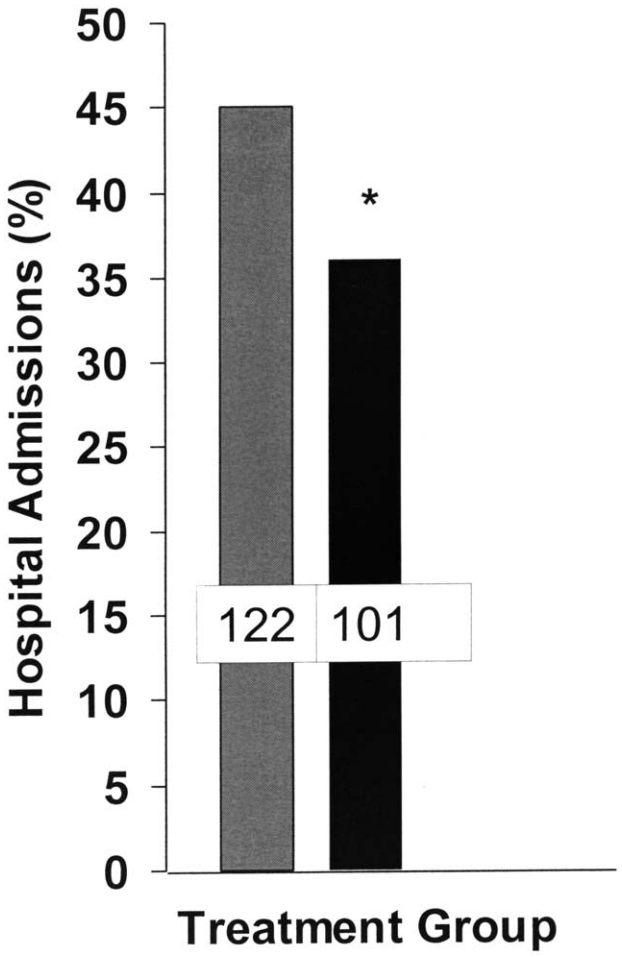

Figure. Hospital admissions in each treatment group, shown as percent of total in each group. Figures on the bars are numbers of patients. *P = .02 compared with racemic albuterol. *Black bar*, Levalbuterol; *shaded bar*, Racemic albuterol.

DISCUSSION

Until recently, optically pure isomers of β-agonists were not available or were not thought necessary for optimum clinical safety or efficacy in acute asthma treatment. The availability of purified (R)-albuterol (levalbuterol) and the Food and Drug Administration's position to quantify the safety of racemic drugs have generated renewed interest in the role of inert isomers. In vitro cellular data implicate (S)-albuterol as a possible cause of airway hyperreactivity, bronchoconstriction, or inflammation[21-24] perhaps induced by stimulating intracellular calcium accumulation and inhibiting adenyl cyclase.[3,7,9,25] However, before our study, clinical data regarding a potential antitherapeutic role for (S)-albuterol were sparse and conflicting.[7,12,26,27]

We report a large, double-blind, randomized trial comparing levalbuterol with racemic albuterol in the management of acute childhood asthma. Substituting levalbuterol 1.25 mg for racemic albuterol 2.5 mg given in a standardized care path for the treatment of acute asthma in the ED resulted in significantly fewer hospital admissions. A 9% reduction in our institution's annual average of 1000 asthma admissions would translate to an approximated annual cost savings of $180,000. The added cost of levalbuterol (approximately $1.25/vial for a mean number of four per patient = $5000.00 to treat 1000 children) would be greatly offset by the savings realized by the reduction in admissions.

For patients admitted to the hospital, we were unable to demonstrate any reduction of LOS, number of aerosols required, or adverse effects with use of levalbuterol. The lack of effect on hospital LOS may be a result of several factors. The higher ED discharge rate in the levalbuterol group could have resulted in sicker patients remaining in this group's hospital cohort. Chronic asthma severity, vital signs, oxyhemoglobin saturation, number of aerosols required, and patients requiring intensified treatment did not differ between study groups, suggesting that the patients were equally ill on ED and hospital admission. Unmeasured factors, such as pulmonary function or atopic status, could have influenced response to treatment. We chose not to include pulmonary function test measures as part of our outcomes because they are rarely used to make a decision regarding hospital admission or discharge and because half of our patients were too young to perform the tests accurately. Second, our hospital LOS is already quite short (~48 hours), and it may be difficult to detect a clinically significant further reduction. There may be a subset of patients who respond more favorably to levalbuterol than to racemic albuterol, and these patients are the ones who improve sufficiently for discharge from the ED. A similar situation is seen with the use of ipratropium in the management of acute asthma; use in the ED results in fewer admissions, but use in the inpatient setting does not shorten LOS.[28,29] We did not demonstrate any reduction in adverse effects (eg, tachycardia or tremor) with use of levalbuterol. Because the adverse effects we recorded are typically related to use of β-agonists, it is not surprising that equivalent doses of R-albuterol (2.5 mg racemic albuterol or 1.25 mg levalbuterol) produced the same adverse event profile.

Children who reported frequent use of racemic albuterol before coming to the ED were almost twice as likely to require hospital admission than those with minimal or no previous albuterol use. It is possible that children with the most severe acute episodes used more racemic albuterol at home. In addition, frequent racemic albuterol use could have resulted in worsening bronchospasm, increased airway hyperreactivity, or decreased response to subsequent racemic albuterol inhalations because of tachyphylaxis. However, the reduction in admission rate between levalbuterol and racemic albuterol was not explained by frequent use of albuterol before receiving ED treatment.

Our data support the use of purified levalbuterol for the ED treatment of acute asthma in children. Confirmation of these results in a similar large, randomized trial will be important.

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